

Applicant : George F. Vande Woude et al.
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In the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

1. *(Currently amended)* A method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of ~~one or more of~~:

(a) one or more of thrombospondin-1 (TSP-1), an anti-angiogenic derivative thereof, or a TSP-1 agonist or mimic; ~~and~~ in combination with

(b) one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; or (iii) both (i) and (ii),
thereby inhibiting said angiogenesis.

2-4. *(Canceled)*

5. *(Previously presented)* The method of claim 1, wherein the inhibitor is a VEGF inhibitor or a VEGF receptor inhibitor.

6. *(Canceled)*

7. *(Previously presented)* The method of claim 5 wherein the VEGF or VEGF receptor inhibitor is selected from the group consisting of an anti-VEGF antibody, an anti-VEGF receptor antibody, a decoy VEGF receptor, VEGF-Trap, a siRNA specific for VEGF, a siRNA specific for VEGF receptor, and a peptidomimetic inhibitor of VEGF receptor activation.

8. *(Previously presented)* The method of claim 7 wherein the VEGF inhibitor is the anti-VEGF monoclonal antibody termed Avastin®.

9. *(Previously presented)* The method of claim 1, wherein the inhibitor is a HGF/SF

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inhibitor or a Met inhibitor.

10. *(Previously presented)* The method of claim 9, wherein the inhibitor is selected from the group consisting of (1) a neutralizing antibody specific for HGF/SF or Met, (2) an HGF/SF antagonist known as NK4, (3) a decoy Met receptor or fragment, (4) a genetically engineered polypeptide derivative of Met with inhibitory activity, (5) a Met-specific siRNA, (6) an inhibitor of the kinase domain of Met, (7) an inhibitor that targets the multi-docking site of Met, and (8) any other agent that decreases HGF/SF or Met expression.

11. *(Previously presented)* The method of claim 1 wherein said providing is to a subject in vivo, which subject is susceptible to, or at risk of, tumor growth or metastasis, or in which subject said tumor growth or metastasis is ongoing.

12. *(Previously presented)* The method of claim 20 wherein said providing is to a subject in vivo, which subject is susceptible to, or at risk of, tumor growth or metastasis, or in which subject said tumor growth or metastasis is ongoing.

13. *(Currently amended)* A method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of one or more inhibitors that target the MAPK pathway and (i) inhibit upregulation of expression or angiogenic activity of VEGF; ~~and/or~~ (ii) inhibit down-regulation of TSP-1; or (iii) both (i) and (ii), thereby inhibiting said tumor angiogenesis.

14-15. *(Canceled)*

16. *(Previously presented)* The method of claim 13, wherein the inhibitor of the MAPK pathway is a MEK inhibitor.

17. *(Previously presented)* The method of claim 16 wherein the MEK inhibitor is anthrax

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lethal factor, another MEK protease, or a small organic molecule.

18. (*Original*) The method of claim 17 wherein the MEK inhibitor is anthrax lethal factor.

19. (*Canceled*)

20. (*Currently amended*) The method of claim 1 which comprises providing effective amounts of: ~~(A)~~ TSP-1 or a TSP-1 agonist or mimic, in combination with ~~(B)~~ one or more of an anti-VEGF antibody, ~~or a~~ VEGF-Trap, ~~and/or~~ ~~(C)~~ or a MEK inhibitor.

21. (*Currently amended*) The method of claim 20 which comprises providing effective amounts of one or more of: (A) TSP-1, (B) an anti-VEGF antibody, ~~and/or~~ or (C) anthrax lethal factor.

22. (*Currently amended*) A composition useful for inhibiting tumor angiogenesis comprising an effective amount or amounts of ~~one or more of~~:

(a) one or more of TSP-1, an anti-angiogenic derivative thereof, or a TSP-1 agonist or mimic; ~~and~~ in combination with

(b) one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met; (ii) VEGF or the VEGF receptor, or (iii) both (i) and (ii).

23-25. (*Canceled*)

26. (*Previously presented*) The composition of claim 22, wherein the inhibitor is a VEGF inhibitor or a VEGF receptor inhibitor.

27. (*Canceled*)

28. (*Previously presented*) The composition of claim 26 wherein the VEGF or VEGF receptor inhibitor is selected from the group consisting of an anti-VEGF antibody, an anti-VEGF receptor antibody, a decoy VEGF receptor, VEGF-Trap, a siRNA specific for VEGF, a siRNA

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specific for VEGF receptor, a peptidomimetic inhibitor of VEGF receptor activation.

29. *(Previously presented)* The composition of claim 28, wherein the inhibitor is the anti-VEGF monoclonal antibody termed Avastin®

30. *(Previously presented)* The composition of claim 22, wherein the inhibitor is a HGF/SF inhibitor or a Met inhibitor.

31. *(Previously presented)* The composition of claim 30, wherein the inhibitor is selected from the group consisting of (1) a neutralizing antibody specific for HGF/SF or its receptor Met, (2) an HGF/SF antagonist known as NK4, (3) a decoy Met receptor or fragment, (4) a genetically engineered polypeptides derivative of Met with inhibitory activity, (5) a Met-specific siRNA, (6) an inhibitor the kinase domain of Met, (7) an inhibitor that targets the multi-docking site of Met, and (8) another agent that decreases HGF/SF or Met expression.

32. *(Previously presented)* A pharmaceutical composition comprising the composition of claim 22, and a pharmaceutically acceptable vehicle or excipient.

33. *(Previously presented)* A pharmaceutical composition comprising the composition of claim 26 and a pharmaceutically acceptable vehicle or excipient.

34. *(Currently amended)* A composition useful for inhibiting tumor angiogenesis comprising an effective amount or amounts of at least two inhibitors that target the MAPK pathway and (i) inhibit upregulation of expression or angiogenic activity of VEGF or its receptor; ~~and/or~~ (ii) inhibit down-regulation of TSP-1; or (iii) both (i) and (ii),.

35-36. *(Canceled)*

37. *(Previously presented)* The composition of claim 34, wherein one of the inhibitors targeting the MAPK pathway is a MEK inhibitor.

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38. (*Previously presented*) The composition of claim 37 wherein the MEK inhibitor is anthrax lethal factor, another MEK protease, or a small organic molecule.

39. (*Canceled*)

40. (*Previously presented*) A pharmaceutical composition comprising the composition of claim 34, and a pharmaceutically acceptable carrier or excipient.

41. (*Previously presented*) A pharmaceutical composition comprising the composition of claim 37, and a pharmaceutically acceptable carrier or excipient.

42. (*Previously presented*) A pharmaceutical composition comprising the composition of claim 38, and a pharmaceutically acceptable carrier or excipient.

43. (*Previously presented*) A pharmaceutical composition comprising the composition of claim 44, and a pharmaceutically acceptable carrier or excipient.

44. (*Currently amended*) The composition of claim 22 which comprises ~~(A)~~ TSP-1 or a TSP-1 agonist or mimic, in combination with ~~(B)~~ one or more of an anti-VEGF antibody, ~~or~~ VEGF-Trap, ~~and/or~~ ~~(C)~~ or a MEK inhibitor.

45. (*Currently amended*) The composition of claim 44 which comprises providing effective amounts of one or more of (A) TSP-1, (B) an anti-VEGF antibody ~~and/or~~ or (C) anthrax lethal factor.

46. (*Previously presented*) A pharmaceutical composition comprising the composition of claim 45, and a pharmaceutically acceptable carrier or excipient.